Acute asthma

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Asthma is the most common medical emergency in children. It is associated with significant morbidity and mortality rates and poses a tremendous societal burden worldwide. Management of the acute attack involves a stepwise approach that includes β-agonist and steroid therapy, the mainstay of emergency treatment. Most patients will respond to this regime and can be discharged from the emergency department. Failure to respond to treatment necessitates hospital admission and sometimes admission to the intensive care unit (ICU). Management in the ICU involves intensification of pharmacologic therapy, including non-standard therapies, in an attempt to avoid intubation and ventilation. When needed, mechanical ventilatory support can be rendered fairly safe with little morbidity if the likely cardiorespiratory physiologic derangements are appreciated and if appropriate ventilatory strategies are used. In the past two decades, the availability of newer potent medications and changes in approach to monitoring and ventilatory strategies have resulted in a decrease in ICU morbidity and mortality rates. Research endeavors are presently underway to further characterize the underlying mechanisms of the disease and are likely to lead to novel therapies. This article reviews the approach to management of acute severe asthma. (Pediatr Crit Care Med 2001; 2:151–163)

KEY WORDS: asthma; children; β₂ agonists; steroids; monitoring; mechanical ventilation; magnesium sulfate; inhaled anesthetics; epidemiology; ketamine

EPIDEMIOLOGY

The second half of the 20th century has seen a rise in the occurrence rate of asthma (1). In the 1970s and 80s, the worldwide occurrence rate seemed to be reaching epidemic proportions together with a rising mortality rate. Many of the important epidemiologic studies that highlighted this problem came from New Zealand where there seemed to be an alarming number of asthma deaths (2–12). A similar trend was seen in North America, although this now seems to be improving (13). Among children, the statistics were also disturbing. Although the overall occurrence rate of asthma in a pediatric population is usually quoted as 5%, a 1992 Australian study of over 8,000 primary school children found an occurrence rate of 17% when screened by spirometry (14). Gerstman (15) also reported increased hospitalization rates in children aged 5–14 yrs, particularly in those in the 5–9 yrs age group between 1980 and 1986. Other studies also highlighted a worrying increase in pediatric mortality rates that were particularly linked to socioeconomic disadvantage (6, 16).

Various explanations for the apparent increase in the mortality rate have been advanced, including environmental pollution, cardiac complications from increased use of inhaled β-agonist therapy, underestimation of the severity of the attack by the patient or parent that led to delays in seeking help, and inadequate treatment by medical practitioners. The β-agonist issue has been the subject of continuing debate because of the increased use of self-medication with inhalers by asthmatics (5, 6, 17–24). The majority of the evidence from these epidemiologic studies suggests that factors other than side effects of sympathomimetic drugs were responsible for the rise in the mortality rate (25). Indeed, the evidence points to undermedication, particularly the underuse of steroids, and lack of recognition of the severity of the attack as being the most important factors (26, 27).

Patients whose symptoms fail to reverse with inhaled bronchodilators and steroids and subsequently require intensive care unit (ICU) admission represent a group with near fatal asthma (NFA) (17, 28–37). These are poorly controlled asthmatics who are at risk for the development of subsequent episodes of NFA and sudden death. Numerous studies have attempted to identify factors common to these patients. They have identified a history of an episode of NFA, previous ICU admission, PaCO₂ >45 torr, and mechanical ventilation as risk factors (38). The use of more than two cannisters of β-agonist therapy per month has also been identified as a marker for increased risk factor in patients with NFA (39). A major recurring theme in all these studies is a lack of recognition of the attack's severity by the patient or the healthcare provider. Lack of heightened patient awareness may be partially explained by studies showing some patients in this group who do not respond to increased resistive loads on the inspiratory muscles (40, 41) and lack the normal chemosensitivity response to hypoxia (42). Inadequate medical treatment caused by patients or health-care provider related factors despite published standards for asthma is a common finding. These include the underuse of steroid therapy and patient noncompliance with therapy (6, 14, 27, 33, 43–48). The underuse of steroids may partly be the result of concerns about side effects in children but also the inability to measure inflammation and, hence, a lack of objective means of titrating steroid dosage (49).

Patients with previous ICU admissions and those requiring mechanical ventilatory support also have an increased risk of a fatal outcome (16, 38, 50). Many of the studies in children emphasize that

parental misunderstanding of the disease's potentially fatal nature and their inability to ensure that children comply with therapy, particularly steroid use, are major risk factors for an adverse outcome, either death or an episode of NFA (16, 45–47, 51–58).

Finally, there is a small subgroup of patients with what was considered to be mild asthma who present acutely with sudden onset of severe airways obstruction (also known as sudden asphyxial asthma) when there is not necessarily a history of an episode of NFA (34, 55, 59–61). This can result in cardiorespiratory arrest in the emergency department or in the home before emergency medical attention is sought (62, 63). If return of spontaneous circulation can be achieved, these individuals frequently require intubation and ventilatory support, albeit for relatively short periods and with lower airway pressures than one would normally expect to see in severe status asthmaticus. Adolescent males who are poorly compliant with medication seem to be a group particularly at risk (1, 61). Post mortem findings in patients who die during an episode of acute asphyxial asthma are different from patients who succumb after the more typical gradual-onset disease. There is a predominance of neutrophils in the airway instead of the numerous eosinophils seen in other asthmatic deaths. There is also a proliferation of mucous glands (64–66)

PATHOPHYSIOLOGY

Understanding of the pathophysiologic changes that affect the cardiorespiratory system is important for implementing a management strategy that will rapidly reverse what can become a rapidly fatal disease. Histopathologic studies in fatal asthma show airway-wall edema, hypertrophy of mucous glands, and plugging of airways with a tenacious mucus consisting of eosinophils, epithelial cell debris, fibrin, and other plasma proteins (67). Mucus plugging, edema of the bronchial mucosa and submucosa, and contraction of airway smooth muscle combine to cause a major impediment to inhaled and exhaled air flow.

One of the most important advances in asthma during the past 20 yrs has been the recognition of asthma as an inflammatory disease. The inflammatory cascade is complex and involves many mediators; however, the principal inciting agents are eosinophils and mast cells and their interaction with the epithelium of the respiratory tract. Mast cells initiate the early response to allergens by degrannulating and releasing stored inflammatory mediators. Antigen-presenting cells facilitate the activation of T lymphocytes by phagocytosing foreign allergenic particles. Activated T cells secrete cytokines including interleukin (IL)-4, IL-5, IL-13, tumor necrosis factor-α, IL-2, and interferon. These promote growth and differentiation of eosinophils and mast cells and their migration into the airway. Immunoglobulin M cells and immunoglobulin B cells change to immunoglobulin E-producing cells, which are typical of atopy. The stimulated epithelial cells produce chemokines, metalloproteases, nitric oxide (NO), and adhesion molecules. These encourage the attraction and binding of eosinophils and T cells to the epithelium and increase squamous degradation. Leukotrienes produced by inflammatory cells are particularly prominent in this inflammatory cascade (68). The understanding of these mechanisms comes largely from bronchoalveolar lavage studies in adults. Although most of this information comes from adult studies, the evidence indicates that it is common to pediatric disease as well (69). Obviously, there are fewer studies in children, but increased numbers of eosinophils and levels of inflammatory markers produced by activated macrophages have been found in bronchoalveolar lavage and sputum samples from symptomatic asthmatic children (70–73). Recognition of the role played by these inflammatory mediators has led to trials of leukotriene receptor antagonists that have shown a bronchoprotective effect in pediatric studies (74–77).

The inability to assess the degree of lung inflammation in children with asthma imposed by limitations on invasive procedures may be resolved by measuring exhaled NO levels. NO has been recognized for some time to have weak bronchodilator properties (78), but its more important asthma management role is the measurement of exhaled endogenous NO as a marker of inflammation in the lung. NO is released from the airway epithelium in response to inflammation acting through inducible NO synthase, the inhibition of which has been shown to decrease bradykinin-induced bronchoconstriction (79). Airway epithelium taken from patients with asthma immunostains strongly for inducible NO synthase (iNOS) (80), and increased levels of exhaled NO have been demonstrated in patients with exacerbations of asthma (81–85), making this a potentially important noninvasive method for monitoring the response to treatment in asthma.

Severe airways obstruction affects lung mechanics, resulting in a dramatic increase in the work of breathing as the patients use their accessory muscles to overcome the resistance to air flow. In severe asthma, transpulmonary pressures >50 cm H_2O are not uncommon (86) Expiration becomes active rather than passive with low flow rates and progressively longer expiratory times. The patient breathes at progressively higher lung volumes to vacillate expiratory gas flow, resulting in the development of dynamic hyperinflation and gas trapping (Fig. 1). If the airway obstruction is not relieved, the enormous increases in respiratory muscle work will eventually result in fatigue and a rapid decompensation. The oxygen consumption of the diaphragm outstrips its supply despite an
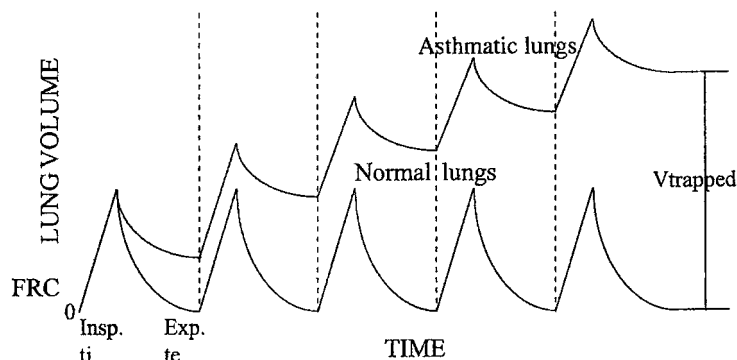

Figure 1. Lung mechanics in asthmatic patients compared with normal. Airway obstruction leads to dynamic hyperinflation caused by inspiration commencing before the termination of the previous expiration. Reproduced with permission from Levy BD: Medical and ventilatory management of status asthmaticus. *Intensive Care Med* 1998; 24:105–117.

increase in blood flow to the muscle (87). The degree of airways obstruction can be measured by spirometry in cooperative children aged ≥ 5 yrs, especially if they have had previous experience with the monitoring device (88, 89). A peak expiratory flow rate of 50%–80% predicted is common in mild to moderate asthma, but severe airways obstruction is associated with levels of <50% predicted.

There are also significant effects on the cardiovascular system. Normally, the negative intrathoracic pressure (ITP) during inspiration augments venous return and right heart filling, resulting in increased output from the right ventricle. Simultaneously, there is a small decrease in output from the left ventricle caused by a combination of leftward shift of the intraventricular septum and an increase in afterload on the left ventricle (90). This response is exaggerated in acute asthma. The large positive ITP associated with expiration causes a marked reduction in venous return and output from the right ventricle, and the high negative ITP causes an increase in left-ventricle afterload. These changes may be detected clinically by an increase in pulsus paradoxus, which in severe asthma is usually >20 mm Hg (91, 92).

The clinical findings commonly seen in acute severe asthma include tachycardia, tachypnea, hyperinflation, wheeze, accessory muscle use, pulsus paradoxus, and diaphoresis. Absence of wheezing may not be a sign of airways obstruction resolution, as the more severe the obstruction, the quieter the chest sounds. The inability to talk in sentences, marked intercostal and subcostal indrawing, and accessory muscle use indicate severe airways obstruction. The extremes of respiratory muscle fatigue are heralded by increasing agitation followed by apathy and somnolence, which precede apnea.

The initial blood-gas derangement seen in acute asthma is a reduction in $PaCO_2$ to <35 torr associated with a period of hyperventilation (93). This rises as airway obstruction worsens, and any increase in $PaCO_2 \geq 40$ torr indicates that respiratory muscle fatigue is developing and should be taken as an ominous sign. Significant hypoxemia is uncommon even in severe asthma, and its presence should alert the physician to the fact that there may be lung collapse from airway plugging or the presence of a pneumothorax. Studies using inert gas techniques have shown that there are significant ventilation/perfusion abnormalities

associated with decreased alveolar ventilation while perfusion is maintained (94). This mismatch may in fact worsen temporarily with the use of β-agonist therapy, which increases perfusion to areas of low ventilation because of its vasodilating effect.

There are also a variety of acid-base abnormalities seen. The most common is an initial respiratory alkalosis caused by hyperventilation. As the airway obstruction worsens, either a metabolic acidosis or a mixed respiratory and metabolic acidosis are common findings (95). Lactic acidosis also develops in association with severe airways obstruction (96, 97). This is caused by a combination of lactate production by the respiratory muscles and tissue hypoxia. Although these abnormalities are frequently seen in severe asthma, few studies have been able to demonstrate a relationship between blood-gas and acid-base derangements and the severity of airways obstruction leading to the necessity for mechanical ventilation.

MANAGEMENT

Emergency Department Assessment and Management

Wheezing is the most common symptom in children attending hospital emergency departments. Although most will improve symptomatically with inhaled β-agonist therapy, more severe cases require more intensive therapy, including oxygen, anticholinergic drugs, and steroids. The safety and efficacy of inhaled β-agonist therapy has been tested in randomized controlled trials in both pediatric and adult asthmatics. Initial concern about potential cardiotoxicity led to them being prescribed on a 2- or 4-hourly basis. The most frequently studied drugs have been salbutamol (albuterol) and terbutaline. The evidence for efficacy strongly supports administration by continuous nebulization without toxicity (71, 98–113). There is also evidence that metered dose inhalers with spacer devices are as effective as wet nebulization in both adults and children (114–116). Side effects such as hypokalemia, tremors, and hyperglycemia are rarely clinically significant with inhaled administration (105, 117, 118).

Two-thirds of asthmatics in an emergency department setting respond variably to albuterol; 1/3 do not respond at all and spend more days in hospital than responders (119). This poor response is thought, at

least in part, to be caused by variation in the β_2-receptor (β_2AR) gene. This intronless gene is located on chromosomal region 5q31-q33 and is 1239 bp long. Seventeen polymorphisms have been identified in the 5' leader cistron, promoter, and coding regions of the β_2AR gene (120–122). The single nucleotide polymorphism (SNP) at amino acid position 16 has been associated with responsiveness to β_2 agonist. Early studies report that asthmatics who are homozygous for arginine at amino acid position 16 (Arg 16/Arg 16) respond better to albuterol than glycine 16 homozygotes (Gly 16/Gly 16) or heterozygotes (Arg 16/Gly 16) (123, 124). Later studies report that Gly 16 homozygotes respond better to β_2-agonist administration than carriers of the Arg 16 allele (125, 126). A more recent study reported that the percentage change in forced expiratory volume in one second (FEV_1) after inhaled albuterol was accurately predicted by the β_2-receptor haplotypes containing 13 different SNPs. No association was found between any of the single SNPs and the response to albuterol (122). It was concluded that the response to albuterol is accurately predicted by β_2AR haplotype; whereas, single site SNPs (e.g., Arg 16 vs. Gly 16) may be poor predictors of β_2 agonist-mediated response. The role that the β_2AR haplotype plays in regulating response to β_2 agonist requires further investigation in large numbers of patients. In the near future, we may be prescribing β_2 agonist to control asthma symptoms based on the patient's AR haplotype.

One of the newer innovations in inhaled β-agonist therapy is the development of levalbuterol (Xopenex, Sepracor Inc., Marlborough, MA). Albuterol is a racemic mixture with a 1:1 ratio of the isomers R-albuterol (levalbuterol) and S-albuterol. The R-iosomer is responsible for the drug's bronchodilator activity, and the S-isomer has been associated with the small increases in the bronchoconstrictive response to methacholine reported with the chronic use of racemic albuterol (127, 128). Levalbuterol inhalation has been approved by the U.S. Food and Drug Administration for prevention and treatment of bronchospasm in patients ≥ 12 yrs of age (129). It is currently available only as a nebulised solution, and there are claims that it is safer than racemic albuterol. *In vivo*, levalbuterol has been reported to have a higher affinity for β_1- and β_2-adrenergic receptors than racemic albuterol (130). The current manufacturer's recommended starting dose is 0.3 mg three times a day every 6–8 hrs by

nebulisation with an increase in dose to 1.25 mg three times a day for patients who do not respond adequately to the lower dose. Although there are some benefits to levalbuterol compared with racemic albuterol, the benefits may not outweigh the additional cost (131).

Inhaled anticholergic drugs produce bronchodilation only by inhibiting cholinergic-mediated bronchospasm. Therefore, anticholinergic drugs are more dependent on the mechanism of bronchospasm than other bronchodilators. However, the majority of studies show that the addition of these drugs produce further increases in bronchodilation when added to β_2 agonist (132–142).

While bronchodilators are used to relieve bronchoconstriction, steroid administration suppresses the underlying inflammation. Oral steroids have also been shown to decrease markers of inflammation in asthmatic children (143) and are the most effective medication for the control of asthma (144). Although anti-inflammatory therapy is the mainstay of treatment in chronic asthma, given that steroids require >6 hrs for maximal effect, there is some dispute as to its effectiveness in reversing the acute attack in the emergency department setting (145–147). Concern about side effects of systemic steroids, particularly growth retardation in children, has led to increased use of inhaled steroids. The use of these preparations have been associated with the suppression of acute attacks, reduction in the occurrence of hospital admissions, and decreased risk of fatal and near fatal asthma in several large case control series of adults with moderate to severe asthma (26, 148–150). In a randomized controlled trial, Singhi (151) has shown that, compared with placebo, inhaled budesonide decreased the necessity for hospitalization in children who had already been treated with inhaled albuterol. However, even when administered by inhalation, these drugs have been shown to have systemic side effects (152, 153) The newest inhaled steroid, fluticasone, has equipotent anti-inflammatory suppression at lower doses. A recent study that compared prednisone (2 mg/kg) with inhaled fluticasone in children presenting to the emergency department with severe asthma who had already received β-agonist therapy showed that prednisone was superior in increasing FEV_1 and decreasing hospital admission rates (154). Part of this decreased efficacy may be explained by severe airways ob-

struction and mucus plugging that frequently result in diminished drug absorption from the respiratory tract. Therefore, preference should be given to systemic steroid administration in intractable status asthmaticus.

Most patients whose symptoms do not fully resolve with emergency department management can safely be managed on general medical wards. Indications for admission from the emergency department are poorly defined but may include the following (155): a) inadequate response to 3–4 aerosol treatments; b) relapse within 1 hr of receiving aerosols and steroids; c) persistent O_2 saturation <91% in room air (156); d) peak expiratory flow rate <10% expected; and e) multiple visits for this episode. Those who deteriorate during their ward admission or who are sicker require intensive therapy and should be admitted to the ICU.

INTENSIVE CARE MANAGEMENT

The criteria for ICU admission of patients with status asthmaticus should include the following: a) history of NFA or mechanical ventilatory support; b) inability to speak in sentences; c) somnolence; d) inaudible breath sounds; e) oxygen requirement to maintain a SaO_2 >95%; and f) $PaCO_2$ >40 torr or acidosis; g) elevated serum lactate levels. The necessity for ICU admission indicates a failure of medical management to reverse bronchospasm and the impending development of respiratory muscle fatigue. It should therefore serve as a signal to intensify treatment to avoid mechanical ventilatory support.

Intravenous β-agonist therapy

Patients may fail to improve symptomatically with continuous high dose inhaled β-agonist therapy because severe bronchospasm and mucus plugging may prevent distal drug delivery by the aerosol route. The alternative route of iv infusion has been used in children with severe asthma for >25 yrs. The original β agonist used was isoproterenol, and there have been a number of case series published where it has been used successfully and with minimal complications in the setting of severe hypercarbic respiratory failure (157–159). However, the pronounced β_1 effects produce a marked tachycardia, and there have been reports

of myocardial ischemia, as measured by elevations in myocardial muscle creatine kinase isoenzymes, in children with status asthmaticus receiving iv isoproterenol (160, 161). Whether the therapy or the severity of the underlying disease is responsible for myocardial muscle creatine kinase isoenzyme elevation is debatable, considering that myocardial ischemic band necrosis has been found in children dying from status asthmaticus who have not received iv β-agonist therapy (162). The more β_2-selective agents, albuterol and terbutaline, are now commonly used with well-documented efficacy and minimal toxicity in both adults and children (157, 163–167). In a randomized clinical trial (RCT) in adults, Cheong and colleagues showed that iv albuterol was more effective than inhaled albuterol in reversing airways obstruction. Similarly, in an RCT comparing the two modes of delivery in children in an emergency department setting, Browne and colleagues (166) found that those receiving the iv preparation could be discharged earlier. Studies such as these are difficult to interpret, as there is no way of assessing effective serum concentrations. However, iv β-agonist therapy can be highly effective in reversing bronchospasm, even in the presence of marked elevations of $PaCO_2$ (157). In our own institution, we have observed that with more aggressive treatment with inhaled salbutamol in the emergency department we see less children admitted to the ICU with severe hypercarbia who used to require the immediate institution of iv β-agonist therapy (168). The important side effects are tremor, tachycardia, and hypokalemia, which are more significant than with the high-dose inhaled drug, and patients receiving iv therapy require potassium supplementation. A widening of the $(A-a)DO_2$ is occasionally associated with improved ventilation to underperfused lung segments (169, 170). In the United States, the only parenteral, pure β_{50} agonist available to the clinician is terbutaline. This is similar to albuterol (salbutamol) in its mechanism of action. It also exists as a racemic mixture but differs from albuterol in that its (+) form is cleared faster than the (−) form; albuterol is the opposite (171).

Other Intravenous Bronchodilator Therapy

Amminophylline. The methylaxanthine group of drugs has been part of the

treatment armamentarium for asthma for >40 yrs, either as oral theophylline for chronic asthma or iv aminophylline for status asthmaticus. In addition to the bronchodilator effect, there is an additional theoretical benefit, as it has both an inotropic effect on the respiratory muscles as well as anti-inflammatory effects (87, 172, 173). However, the window between therapeutic effect and toxicity is relatively narrow, and this can lead to serious side effects that include fever, excitability, and seizures (174–176). There have been well-documented cases of brain damage occurring secondarily to theophylline overdose. Given this fact, one has to carefully evaluate the risk vs. any additional benefit of using such a drug in patients already receiving high-dose bronchodilator therapy. Most randomized trials in adults and children with acute asthma would suggest that there is no benefit (177–180). However, one randomized trial in children admitted to ICU with severe asthma reported improvement in air flow obstruction when aminophylline was added to β-agonist therapy (181) but minimal difference to the ICU length of stay. Given the potential for toxicity and the marginal benefit, there does not seem to be a rationale to recommend continuing to use this drug as a standard therapy for severe asthma. It is, however, well recognized that theophylline is still used as a first line drug in many parts of the world. It has fallen into disfavor in North America and is only used occasionally in children who are responding poorly or fail to respond to maximal β-agonist therapy. Although cost may be an important determinant of whether or not it is used, the added cost of monitoring the serum theophylline level may not result in any advantage as compared with the high doses of β-agonist therapy.

Magnesium Sulfate. Although a case report of 60 yrs ago (182) suggests that magnesim has bronchodilator effects and a role in the treatment of asthma, it was not until 1989 that Skobeloff and colleagues (183) reported that magnesium sulfate administered in asthmatics who were refractory to albuterol produced a significant improvement in peak expiratory flow rate and reduced costs of hospitalization. Magnesium, a physiologic calcium antagonist, is known to have a direct effect on calcium uptake in smooth muscle, resulting in muscle relaxation. There are a significant number of published case series and randomized trials

that report improvements in bronchospasm when it has been used in either the emergency room setting (184–186) or in the ICU in patients receiving mechanical ventilation (187, 188). There is also evidence that it is as effective as albuterol when administered by inhalation (189), and one study has reported that albuterol nebulised with isotonic magnesium produced more effective bronchodilation when compared with saline (190). Systematic reviews of the limited number of RCTs of magnesium sulfate in exacerbations of acute asthma have focused on the effect on FEV_1 and its effectiveness in reducing the number of asthma admissions. Their conclusions were that there is insufficient evidence to support its routine use in severe asthma but that it is safe and seems to be effective in some cases (184, 191, 192). The most commonly reported side effect is hypotension.

Bicarbonate. Although a case Another somewhat controversial therapy is the use of iv bicarbonate in severe asthma. The rationale for its use is based on evidence that acidosis (pH, <7.2) antagonizes the effect of endogenous catecholamines and exogenously administered β-agonist therapy. The potential downside is that the CO_2 released when bicarbonate is metabolised will lead to further hypercarbia. In our experience, the correction of the acidosis results in an increase in alveolar ventilation that more than offsets the increase in $PaCO_2$ levels. There are several case reports and case series of improvements in symptomatic bronchospasm and reductions in $PaCO_2$ in patients with severe asthma whether they were receiving ventilatory support or breathing spontaneously (193–196).

Ketamine. Ketamine is a dissociative anesthetic agent whose bronchodilating effects are considered to be a combination of a drug-induced increase in circulating catecholamines, direct muscle relaxation, and inhibition of vagal tone (197, 198). Ketamine is the ideal sedative for intubation and ventilatory management of an asthmatic patient. There is controversy regarding ketamine administration in nonintubated patients because of fear that the increases in pulmonary secretions, occasional laryngospasm, and the need for benzodiazipine pretreatment may complicate asthma management (199). However, experience using ketamine, consisting of case reports demonstrating safety of management in intensivist-staffed ICUs have dispelled most of

these fears (200–204). In all cases, ketamine should only be used in the ICU with close monitoring and readiness to intervene to support ventilation if necessary.

MECHANICAL VENTILATORY SUPPORT IN ASTHMA

Patients admitted to ICU whose bronchospasm fails to respond to the measures outlined above and who develop increasing respiratory insufficiency require mechanical ventilatory support. There are no clearly defined markers for necessity to intervene, and the decision is usually based on a clinical judgment of increasing fatigue. Noninvasive ventilation (BiPAP) may be effective in reversing this if initiated early in the process, (205) but it is difficult to use in children unless the child is cooperative (206). A rising $PaCO_2$, failure to maintain oxygenation saturations >95%, a worsening metabolic acidosis, and a decreasing level of consciousness are all signs that may herald a respiratory arrest and the urgent need to intubate and ventilate.

The intubation of a patient with severe asthma poses a significant challenge to the intensive care physician. The child is frequently borderline hypoxic, acidotic, struggling, and at risk of aspiration. Therefore, a rapid sequence induction of anesthesia followed by muscle relaxation is necessary to secure the airway. The options for induction include opiates with benzodiazepines, thiopentone, propofol, or ketamine. Narcotics and thiopentone have been reported to induce histamine induced bronchospasm, although this concern is more theoretical than real. Propofol and ketamine can produce bronchodilation (203, 207–210). Our preference is to use ketamine intravenously supplemented with a benzodiazepine to reduce the risk of hallucinations. This is followed by suxemethonium with gentle application of cricoid pressure on relaxation. After placement of a cuffed tube, care should be taken not to hyperventilate, as is common practice after many emergency intubations. Moreover, a common mistake is the failure to initially administer a long-acting paralyzing agent until ventilation is well establised. Failure to do this may result in coughing and gagging with accompanying desaturation or barotrauma. A decrease in saturation after intubation may be caused by a decrease in cardiac output with gas
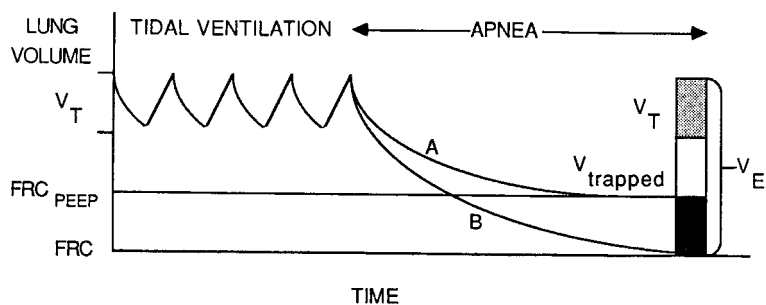
Figure 2. Schematic representation of the measurement of end-expiratory volume (VEI) with and without peak end-expiratory pressure in ventilated asthmatic patients. Reproduced with permission from Tuxen DV: Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis* 1989; 140:5–9.

trapping and high ITP rather than inadequate ventilation in this setting.

The correct choice of ventilator variables in severe asthma must take into account the pathophysiologic derangement within the lung. This means that allowing for an adequate expiratory time is key to avoiding gas trapping. Attempts to achieve a normal $PaCO_2$ will likely result in an unacceptably high plateau pressure (peak airway pressure at the end of a 0.5-sec inspiratory hold plateau pressure) and increased risk of barotrauma. Barotrauma will increase the duration of ventilatory support and may result in poorer outcomes. These were reflected in a case series of mechanical ventilatory support in severe asthma published in the 1970s and early 80s that reported mortality rates of up to 30% (211–217). Some of the deaths in these studies were the result of technical problems with the ventilator, inappropriate attempts to sedate patients with severe airways obstruction leading to cardiorespiratory arrest, and airleaks from the lung resulting in mediastinal and subcutaneous emphysema and pneumothorax (54, 218). In all these studies, very high airway pressures were used to normalize $PaCO_2$. A major change in ventilator management occurred after the publication of the landmark article by Darioli and Perett (219) in 1984. They adopted the approach of using a lower tidal volume of 8–12 mLs/kg in an attempt to limit peak airway pressure to ≤50 cm H_2O. If this limit could not be achieved, they would reduce tidal volumes further and allow $PaCO_2$ to increase rather than exceed their target positive inspiratory pressure (PIP). There were no deaths in their series despite hypercarbia and acidosis. This was one of the first publications that spawned the permissive hypercapnia approach to ventilation. It also served to focus attention on what are

the most important objectives in ventilatory support of a patient with asthma. These include the reversal of hypoxemia, relief of respiratory muscle fatigue, maintenance of a level of alveolar ventilation compatible with a compensated pH, and avoidance of levels of ITP that would adversely affect cardiac output. Oxygenation is rarely a problem except in the most severe cases and unless there is a major lung collapse or pneumothorax. Relief of respiratory muscle fatigue is achievable with a judicious use of sedatives and minimal amounts of neuromuscular blockade because of the potential for the development of myopathy (220–222). However, the elevated $PaCO_2$ levels may mandate the use of muscle relaxants in the first instance to abolish the respiratory drive. Continuous infusions of benzodiazepams should be used to ensure adequate sedation.

Ventilation Mode: Pressure or Volume?

The modes of ventilatory support available in severe asthma are either volume or pressure preset. Most of the reported experience has been with the volume option, but most of these have been adult series using ventilators that did not have the pressure preset option. Some of most important studies that have led to better informed choices of ventilatory settings have been observations of respiratory mechanics published in a series of papers by Tuxen and colleagues (223–226) in which they evaluated factors such as inspiratory gas flow, respiratory rate, tidal volume, peak end-expiratory pressure (PEEP), and peak (plateau) airway pressure using volume ventilation. They used end inspiratory lung volume, measured by disconnecting the patient for 40 secs after a tidal inspiration as an index of

dynamic hyperinflation (Fig. 2). They found that this instead of PIPplat revealed the detrimental effects of PEEP and dynamic hyperinflation, which correlates with the degree of pulmonary barotrauma and adverse effects on hemodynamics. From these studies, they concluded that the optimal settings that would minimize these adverse effects were small tidal volumes, a long expiratory time produced by a low-minute ventilation, and a high inspiratory gas flow.

How does this translate into selecting ventilatory settings at the bedside? There is general agreement that slow respiratory rates (<16/min) and a PIP of ≤35 cm H_2O and zero PEEP fit best with their recommendations. The volume-preset mode can provide a high inspiratory gas flow and is commonly used with a shortened inspiratory time to keep PIPplat to a minimum. This mode of ventilatory support also provides a constant tidal volume as long as there is no substantial leak around the endotracheal tube. Resolution of airway obstruction can be monitored by a decrease in airway pressure. In a case series from this institution published 10 yrs ago, we used volume ventilation with a tidal volume of 8–12 mLs/kg, which usually resulted in a PIP of 40–45 cm H_2O (227). There was no mortality, minimal morbidity, and the duration of ventilatory support was <48 hrs in 75% of the patients. No attempt was made to reduce $PaCO_2$ levels, which were as high as 60 torr. Other pediatric series have reported equally good outcomes using this controlled hypoventilation approach (228, 229).

With the decreasing emphasis on normalizing $PaCO_2$ levels, many are now choosing the pressure-ventilation mode. This provides a high initial gas flow with rapid deceleration. Pressure can be limited with a prolonged expiratory time (206). Although this would restrict PIP-plat, the downside would be that there could be major changes in alveolar ventilation as airway resistance changed. A further option, available on some ventilators, is to use pressure-regulated volume control, which combines some of the advantages of both pressure and volume, namely a high inspiratory gas flow and an assured tidal volume that is pressure limited.

Because the evidence for benefit of one mode over another is weak, no firm recommendation can be made on whether to choose pressure or volume. The best practice is to use physiologic

variables to guide ventilatory settings. Many of the newer generation of ventilators have graphic programs that analyze gas flow as well as pressure and volume. These can be used advantageously to determine whether expiratory gas flow is complete before the onset of the next inspiratory cycle. If this feature is not available, auscultation of the chest during the expiratory cycle can help to determine whether the expiratory time is adequate. The amount of auto-PEEP can be measured with an end expiratory hold for 2 secs. The shape of the expiratory capnogram can also provide useful graphic information as to the adequacy of lung emptying (206).

The necessity to intervene with mechanical ventilatory support should be a signal to increase therapy. The goal should be to intensify pharmacotherapy to shorten the period of ventilation to the minimum. This requires careful drug titration as well as attention to the ventilatory strategy to avoid either an adverse outcome or unecessary time on the ventilator. β-agonist therapy should be increased, switching to an iv preparation or, in intractable cases, adding nonstandard bronchodilator therapies. These would include bolus doses of magnesium sulfate (230–232) and inhalation anesthetic agents. Ether, isoflurane, ethrane, and halothane have all been used to treat ventilated patients with intractable bronchospasm (233–240). Their maximum effect is of a relatively short duration. Their major side effects are hypotension caused by myocardial depression or peripheral vasodilation. Central venous pressure monitoring may be necessary to determine whether inotropic support or fluid bolus therapy is required.

Heliox has also been used to treat asthma based on the rationale that its lower density will be beneficial in airways obstruction (206, 241–244). There is evidence from case series and one RCT that it improves airways obstruction in asthmatics in the emergency department (245–247). In ventilated patients, its usefulness may be limited by the need for high levels of FIO_2. NO has weak bronchodilating properties and has been used successfully to treat a patient with severe asthma who was receiving ventilatory support (248). Patients with hypoxemia caused by lung collapse with airway plugging may benefit from the instillation of deoxyribonuclease, a drug that is commonly used to treat patients with cystic fibrosis, into the trachea (249). Finally, if all else fails, extracorporeal membrane oxygenation may be life-saving (250–252).

Once bronchospasm has been reversed and PIP is <30 cm H_2O, sedation should be discontinued, the patient should be switched to pressure support, and weaning should be accelerated toward an early extubation as long as there is no residual muscle weakness. Few patients require prolonged weaning.

The implementation of more physiologically based principles in the management of mechanical ventilatory support in asthma has resulted in an ICU mortality rate of nearly zero in this group of patients (227, 228, 253–257). The few fatalities now reported in these patients occur in those with sudden-onset severe asthma who have a cardiorespiratory arrest before hospital admission (258).

FUTURE DIRECTIONS

It is obvious that our approach to asthma is suboptimal, as judged by the mortality and morbidity rates associated with this disease. However, there are reasons for optimism in that research is now underway to further characterize the pathophysiology of the disease and tailor treatment recommendations. For example, it is recognized that the bronchodilatory responses depend on specific β-agonist receptor genotype in asthma (123, 125). Recognizing that differences in β_2 genotypes contributes to the variability in FEV_1 response to albutereol are leading to several pharmacodynamic studies and investigations of alternative treatments such as leukotriene inhibitors (74–77). Recognition that the higher prevalence and greater morbidity and mortality rates of asthma among black children is not caused by socioeconomic status and lack of access to care as prevailing wisdom suggested (259, 260) is lending support to further genetic studies to pinpoint asthma susceptibility loci (261). Moreover, studies into specific NO synthase polymorphism as contributors to asthma severity in African Americans as reported for cardiovascular diseases are underway (262). The findings of the studies are likely to revolutionize our treatment of asthma. For instance, it is likely that in the near future asthmatics will be characterized by their specific β-receptor subtype and nitric oxide synthase genotype. Treatment can then be tailored with the expectation of good disease control rather than the trial and error approach that has been commonly used. Of great relevance in developing countries is the inability to afford commercially available spacers to provide delivery of inhaled β agonists. This has resulted in increased morbidity and mortality rates from asthma. However, innovative researchers in these locales are searching for cheap and readily available alternative delivery systems. Research using inexpensive local alternatives such as styrofoam cups and soft drink bottles in several developing countries are yielding optimistic results that these alternatives are effective (263–266).

SUMMARY

Although there has been an alarming increase in the occurrence rate of asthma, there is now a much better understanding of the pathophysiology of the disease, particularly the importance of inflammation. The emphasis in treatment remains on the aggressive use of inhaled β-agonist and steroid therapy to abort the acute attack and decrease both the mortality rate and the need for hospitalization. Finally, there have been significant advances in ventilatory management that have led to improved outcomes in those patients presenting with severe respiratory failure.

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